Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia

Neonatal academic hospitals' consensus guidelines for South African hospitals and primary care facilities

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The purpose of this document is to address the current lack of consensus regarding the management of hyperbilirubinaemia in neonates in South Africa. If left untreated, severe neonatal hyperbilirubinaemia may cause kernicterus and ultimately death and the severity of neonatal jaundice is often underestimated clinically. However, if phototherapy is instituted timeously and at the correct intensity an exchange transfusion can usually be avoided. The literature describing intervention thresholds for phototherapy and exchange transfusion in both term and preterm infants is therefore reviewed and specific intervention thresholds that can be used throughout South Africa are proposed and presented graphically. A simplified version for use in a primary care setting is also presented. All academic heads of neonatology departments throughout South Africa were consulted in the process of drawing up this document and consensus was achieved.

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The range of different thresholds for the initiation of phototherapy and exchange transfusion in newborn infants in South Africa reflects the same lack of consensus that exists worldwide.[1] There are also no local evidence-based guidelines on how to manage infants who are jaundiced but do not require phototherapy, and there is a worrying misconception among some medical staff that a single total serum bilirubin (TSB) level below the phototherapy threshold is sufficient basis to discharge infants with only visual review thereafter.

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A national guideline for the management of neonatal jaundice will help facilitate uniform care and admission criteria and could ultimately improve the care of jaundiced neonates.

This document is the result of collaboration with the heads of neonatal departments of all South African medical faculties.

International recommendations for the use of phototherapy and exchange transfusion in jaundiced term and near-term infants

The aim of phototherapy and exchange transfusion is to avoid kernicterus. The pathological definition of kernicterus is gross yellow staining in the brainstem nuclei with microscopic evidence of neuronal damage.[2] However, in the literature reviewed, kernicterus was defined by any of the following: postmortem pathological findings, acute clinical findings (bilirubin encephalopathy) and typical chronic neurological sequelae.

In 1952, before the use of phototherapy was established, Hsia *et al*.[3] studied 229 infants with erythroblastosis fetalis. They demonstrated that when TSB levels exceeded 340 µmol/l, the risk of kernicterus increased significantly and at TSB levels above 510 µmol/l the risk rose to 50%, despite exchange transfusion. When they introduced a policy of attempting to keep the TSB level below 340 µmol/l using exchange transfusion, there were no cases of kernicterus in 200 consecutive cases. Twenty years later, Oski and Naiman[4] published a nomogram that was constructed by Diamond and Allen, specifically for use with infants with erythroblastosis fetalis. Despite the introduction of phototherapy, the TSB level above which exchange was obligatory remained at 340 µmol/l for both term and preterm infants.

By 1979 the use of phototherapy was well established. Cockington[5] used Diamond and Allen's nomogram as a basis for recommendations on when to perform exchange transfusion and added recommendations on when to initiate phototherapy. Despite the availability of phototherapy, he did not raise the level of obligatory exchange. However, following a recommendation by Karabus,[5,6] Cockington devised different thresholds according to birth weight and age in hours. He did not suggest different thresholds for infants with other risk factors.

Although he did not define the recommended irradiance level of the phototherapy it must have been low because he used a bank of only 12 white fluorescent bulbs. However, his small study of 85 cases across all weight groups showed the suggested phototherapy intervention levels to be effective at preventing the need for exchange transfusion in most infants. Cockington's charts remain in use in some centres in the UK today[1] and they are recommended in a definitive local text by Harrison.[7]

Since Cockington, there have been several other recommendations, all based on limited evidence.[1] A recent, comprehensive review[8] of the available evidence for the management of jaundiced term and near-term (> 34 weeks' gestation) infants was published in 2004 by Stanley Ip, and the American Academy of Pediatricians' (AAP) Subcommittee on Hyperbilirubinemia.

The report concluded that kernicterus has a 10% mortality and 70% morbidity risk versus the risk of permanent sequelae caused by exchange transfusion of 5 - 10%. The reviewed studies of infants who already have kernicterus showed that the vast majority of term and near-term infants with kernicterus and co-morbidity (e.g. sepsis, haemolysis) had a peak recorded TSB of > 342 µmol/l. The infants with kernicterus who had no associated co-morbidity showed a higher peak with a TSB range from 385 to 923 µmol/l. Although acute kernicterus (bilirubin encephalopathy) can be completely reversible if treated by exchange transfusion,[9] only 14% of the group reviewed by Ip *et al*. are known to have survived without chronic sequelae. However, much of the data were missing, so this number may be higher.

Contrary to the retrospective review of infants with kernicterus, the review of prospective studies of all infants with hyperbilirubinaemia showed many infants who did not develop kernicterus, with bilirubin levels well over 428 µmol/l. There was also no consistent association between peak TSB and intelligence quotient, long-term neurological problems or permanent hearing loss. However, the data from the largest contributing study,[10] the Collaborative Perinatal Project (CPP), were subsequently shown[11] to be significantly confounded by the beneficial effect of exchange transfusion that was done in 53% of infants with TSB > 342 µmol/l and this would have included virtually all infants with peak TSB > 428 µmol/l (phototherapy was not yet widely available at the time of data collection, 1959 - 1966). Thus, while most infants with kernicterus have TSB > 342 µmol/l, most infants with TSB > 428 µmol/l do not have problems if the level of bilirubin is reduced rapidly (i.e. via exchange transfusion).

Ip's review formed the basis of the updated AAP recommendations published in 2004.[12] These recommendations differed from the 1994 AAP recommendations (Table I)[13] in that the TSB levels were plotted onto an hour-based curve (Figs 1 and 2). The availability of high-intensity phototherapy and the acknowledgement of specific risk groups, resulted in relatively raised phototherapy and exchange transfusion thresholds for well term infants and different intervention levels for infants at risk. High-intensity phototherapy is recommended as a first-line intervention, but immediate exchange is recommended if TSB levels at presentation are greater than 85 µmol/l above the exchange threshold or if bilirubin levels are not expected below the exchange threshold within 6 hours.

The approach to the jaundiced term and near-term infant has been further refined by Bhutani *et al*.,[14] who derived an hour- and age-based bilirubin centile chart from a study of 17 854 live births between 1993 and 1997 (Fig. 3). This chart assigns risk of progression to higher levels depending on the current level of the TSB. Thus 39.5% of infants with TSBs in the high-risk zone after age 18 hours will remain in that zone 24 hours later, 12.9% of infants in the high-intermediate zone will cross into

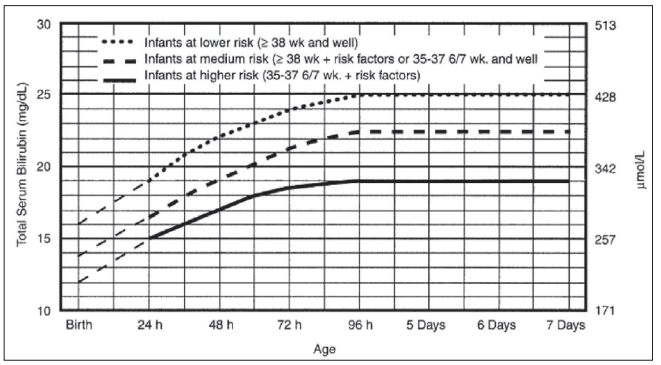

Fig. 1. Exchange transfusion thresholds recommended by AAP, 2004[12] (reproduced with permission).

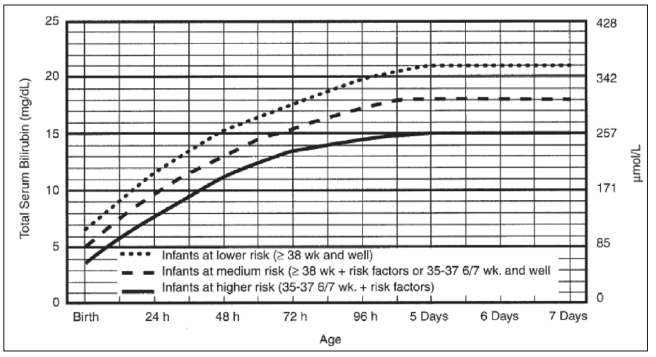

Fig. 2. Phototherapy thresholds recommended by AAP, 2004[12] (reproduced with permission).

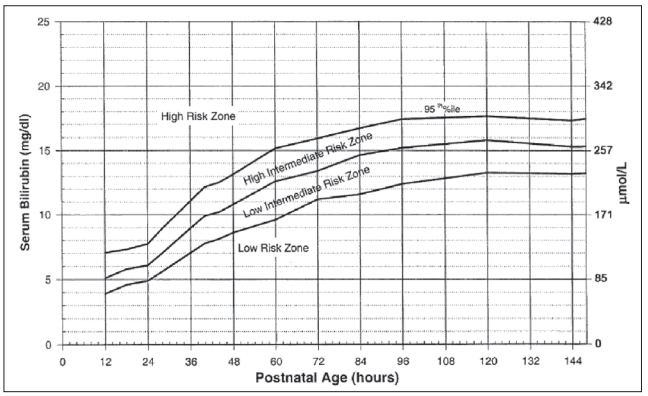

Fig. 3. Risk designation of term and near-term newborn infants, based on their hour-specific bilirubin levels[14] (reproduced with permission).

the high-risk zone and 2.2% of infants in the low-intermediate zone will cross into the high-risk zone. None of the infants in the low-risk zone will cross into the high-risk zone. This information assists discharge planning for infants who are jaundiced, but do not require phototherapy. The application of this chart according to risk zone is recommended[15] as follows: (*i*) high-risk zone – start phototherapy if threshold reached. Repeat TSB in 6 - 12 hours; (*ii*) high-intermediate risk zone – repeat TSB within 24 hours; (*iii*) low-intermediate risk zone – repeat TSB within 48 hours; (*iv*) low-intermediate risk zone – clinical evaluation only within 48 hours.

International recommendations for the use of phototherapy and exchange transfusion in jaundiced low-birth-weight and very-low-birth-weight infants

The management of low-birth-weight infants is less clear than that of term infants. Cockington's guidelines[5] extended to infants less than 1 500 g but had no further weight subdivisions. In 1985, the National Institute for Child Health and Human Development (NICHD) published thresholds[16] for infants who weighed less than 1 250 g, but they did not provide a time component (Table II). In 1994, Watchko and

Table I. AAP 1994: Management of hyperbilirubinaemia in the healthy term newborn[13]

	TSB level (µmol/l)			
Age (h)	Consider phototherapy	Phototherapy	Exchange transfusion if intensive phototherapy fails	Exchange transfusion and intensive phototherapy
< 24	Jaundiced infants this age are not considered healthy and require further evaluation			
25 - 48	≥ 170	≥ 260	≥ 340	≥ 430
49 - 72	≥ 260	≥ 310	≥ 430	≥ 510
> 72	≥ 290	≥ 340	≥ 430	≥ 510

Table II. Varying recommendations for exchange transfusion in preterm infants: Birth weight (g) v. bilirubin (µmol/l) thresholds[16,18,20-23]

Birth weight, g (gestation)	NICHD 1985	Ahlfors 1994	Maisels in Avery *et al.* 1999	Ives in Rennie and Roberton 1999	Cashore 2000	NICHHD Trial 2002
Risk factor adjustment	Subtract 40 µmol/l	Subtract 40 µmol/l	'Use lower values'	Subtract 40 µmol/l	'Use lower values'	Not specified
500 - 749	220	220	220 - 275	200	204 - 255	220
750 - 999 (< 28 wks)	220	220	220 - 275	200	255	255
1 000 - 1 249 (28 - 31 wks)	220	220	220 - 275	250	255 - 306	Not specified
1 250 - 1 499 (32 - 34 wks)	255	255	220 - 275	300	289 - 340	Not specified
1 500 - 1 999 (35 - 36 wks)	289	290	275 - 300	350	Not specified	Not specified

* wks = weeks.